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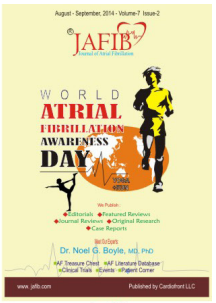

Clinical Relevance Of Systematic CRT Device Optimization

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Abstract

Cardiac Resynchronization Therapy (CRT) is known as a highly effective therapy in advanced heart failure patients with cardiac dyssynchrony. However, still one third of patients do not respond (or sub-optimally respond) to CRT. Among the many contributors for the high rate of non-responders, the lack of procedures dedicated to CRT device settings optimization (parameters to regulate AV synchrony and VV synchrony) is known as one of the most frequent.

The most recent HF/CRT Guidelines do not recommend to carry-out optimization procedures in every CRT patient; they simply state those procedures "could be useful in selected patients", even though their role in improving response has not been proven.

Echocardiography techniques still remain the gold-standard reference method to the purpose of CRT settings optimization. However, due to its severe limitations in the routine of CRT patients management (time and resource consuming, scarce reproducibility, inter and intra-operator dependency), echocardiography optimization is widely under-utilized in the real-world of CRT follow-up visits. As a consequence, device-based techniques have been developed to by-pass the need for repeated echo examinations to optimize CRT settings.

In this report the available device-based optimization techniques onboard on CRT devices are shortly reviewed, with a specific focus on clinical outcomes observed in trials comparing these methods vs. clinical practice or echo-guided optimization methods. Particular emphasis is dedicated to hemodynamic methods and automaticity of optimization algorithms (making real the concept of "ambulatory CRT optimization"). In fact a hemodynamic-based approach combined with a concept of frequent re-optimization has been associated - although retrospectively - with a better clinical outcome on the long-term follow-up of CRT patients. Large randomized trials are ongoing to prospectively clarify the impact of automatic optimization procedures.

Twenty Years Of CRT: A Story Of Success

The concept of Cardiac Resynchronization Therapy (CRT) was first introduced twenty years ago, by proposing the implantation of a 4-chamber pacing system[1] in a patient with permanent pacing indications affected by severe dilated cardiomyopathy, in an attempt to improve cardiac output by constantly pacing the ventricles. Beside optimal medical treatment, the modern concept of CRT (bi-ventricular pacing delivered by using various techniques) is widely recognized and adopted as a first-line therapy in patients with moderate-to-severe heart failure (HF) and evidence of cardiac dyssynchrony.[2,3] In selected group of HF patients, today well-identifiable by simply applying Guidelines directives, CRT has been shown highly beneficial in improving prognosis (death and HF hospitalizations), quality of life (QoL), NYHA functional class and exercise capacity (walk test and cardiopulmonary performance). Significant results have been also obtained in specific subgroups of HF patients, where CRT indications are less clearly established[2] (low level of evidence), due to lack of concordant data, small populations and/or few exploring trials.

Disclosures:
None.

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The Grey Areas In CRT

Although recent Guidelines and Consensus Documents[2,3] further refined selection and management criteria for patients treated with CRT, a remarkable rate of "non-responders" (NR) is still generally observed in clinical reports. The reported rate of NR ranges between 20% and 45% according to different criteria (clinical, hemodynamic, neuro-humoral, combined) and timelines considered to define "CRT response".[3] It is usually "common sense" that approximately a third of patients treated with CRT do not respond (or do sub-optimally respond) to CRT.[4]

Meta-analyzing data from most recent clinical reports, major determinants for improving CRT response could be identified:[4] patient selection (how to predict CRT response basing upon clinical/hemodynamic variables), implantation techniques (how to customize leads implantation/positioning to enhance CRT effects), patient management during follow-up (how to optimally manage patients once implanted).

This report will focus on a critical review of patient-management strategies during follow-up (FU), paying special attention to CRT device settings, as it is acknowledged[5] that one of the most important contributing factor affecting the rate of NR in clinical practice is the lack of periodic procedures to optimize systolic and diastolic performances by fine-tuning the atrioventricular delay (AVD) and the right-vs.-left ventricular delay (VVD).

The final goal would be to rigorously define protocols and methods

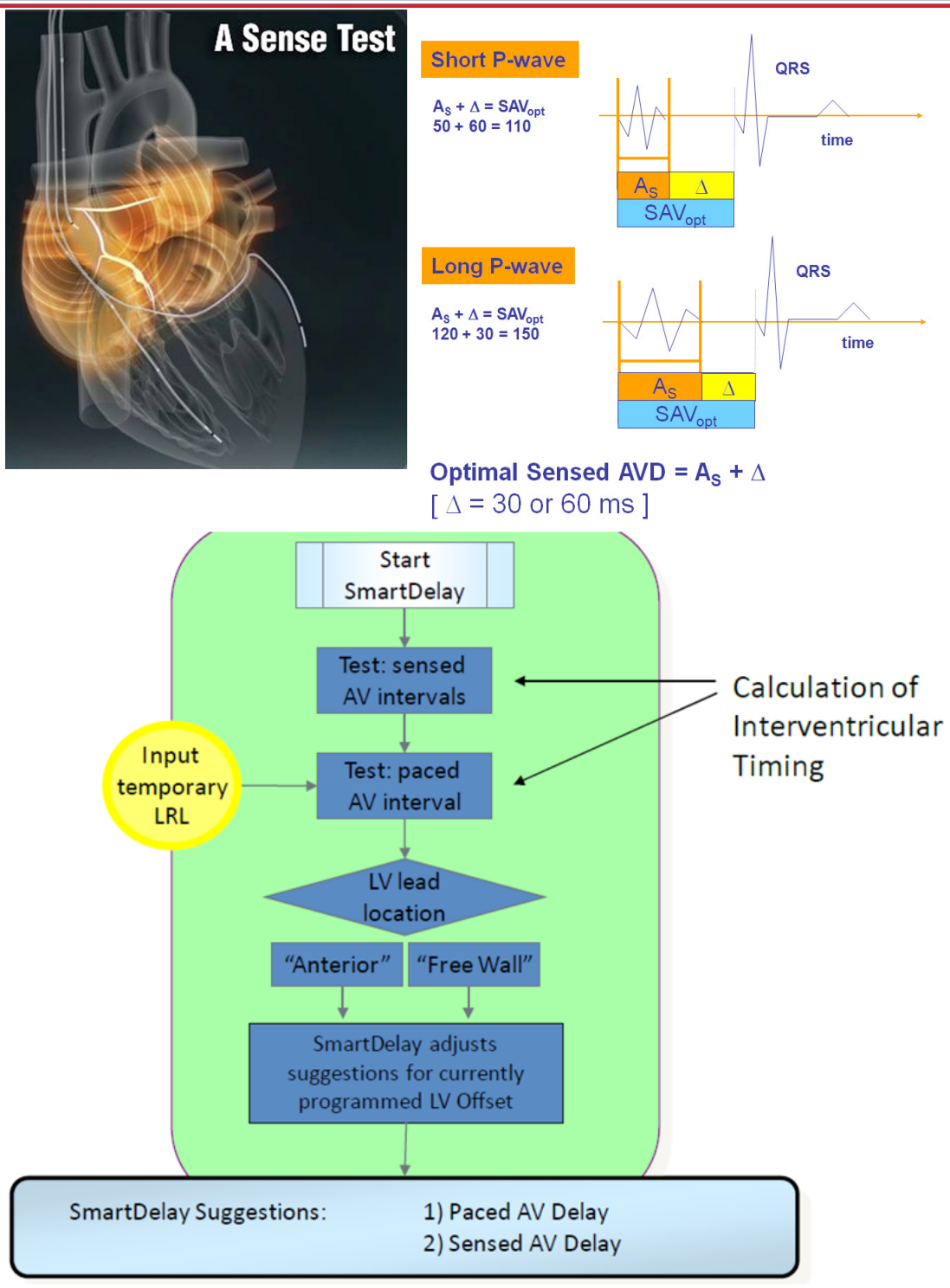

Figure 1: **Top panel: QuickOpt IEGM method to determine the optimal sensed AVD value**
Bottom panel: SmartDelay IEGM method to determine the optimal paced and sensed AVD values; LRL = Lower Rate Limit (basic pacing rate)

for CRT settings optimization able to provide clinicians with an acceptable degree of clinical efficacy during FU.

How To Optimize CRT Device Settings

Echocardiographic Methods

The universally acknowledged gold-standard technique to optimize CRT settings is an hemodynamic method, namely the trans-thoracic echocardiography. By direct visualization of blood flows, it allows to optimize filling (trans-mitral) and ejection (trans-aortic) patterns among many potential combinations of AVD and VVD values, in atrial sensed or paced conditions.

Several studies, although small, consistently show concordant data about the fact that echocardiography methods lead to acute (or short-term FU) hemodynamic benefits. However, there is no convincing prospective evidence about the long-term effects (neither clinical, nor hemodynamic) associated with repeated optimization procedures over-time. It is not clear whether frequently optimizing CRT settings could translate evident acute/short-term hemodynamic benefits into persistent clinical benefit.[6]

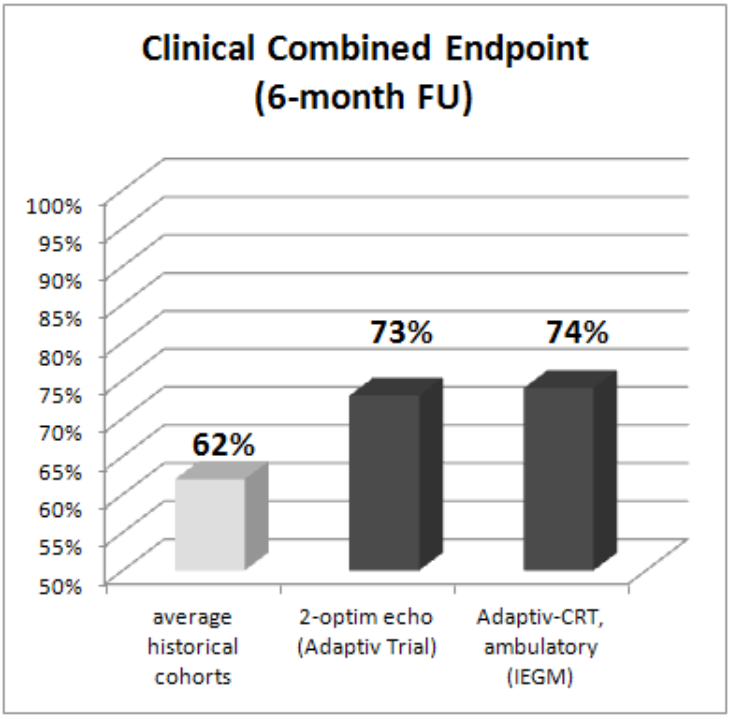

Figure 2: **Response Rate at 6-month follow-up (Packer's clinical combined endpoint) observed in the Adaptive-CRT trial. Dark-grey hystograms: prospective randomized comparison (non-inferiority). Light-grey hystogram: average response rate from historical CRT cohorts.**

Several echocardiography optimization protocols have been proposed to optimize CRT settings (formulas and iterative methods), often leading to unsatisfactory performances - sometimes even to discordant results - invariably showing remarkable limitations: time- and resource-consuming (manpower/equipments), non-reproducible outcomes (inter- and intra-operator dependency), optimization only with resting patients, need to be frequently repeated.[7]

The well-known limitations of echocardiography optimization methods[8] boosted the need to develop alternative methods, able to simultaneously overcome those limitations and simplify the clinical practice of CRT patients management. The simplest approach to this problem is to get rid of the echocardiographer's collaboration, and to take direct advantage of the CRT device itself to easily repeat settings optimization procedures basing upon endocardial electrograms or hemodynamic signals directly processed by the device.

"Device-Based" Methods

Algorithms Based On Intracardiac Electrograms (IEGM)

Three IEGM-based algorithms for CRT optimization are today available: QuickOpt (St. Jude Medical), SmartDelay (Boston Scientific), Adaptive-CRT (Medtronic). Through direct measures on atrial, right- and left-ventricular EGMs, these algorithms use predefined formulas to process "electrical activation delays" between cardiac chambers (upon spontaneous or paced rhythm) in order to identify (and program) the best combination of AV and VV timings to fix conduction defects (in other words they work on the basis of a predefined electromechanical model of the cardiac cycle).

In-depth technical description of the IEGM-based methods, and the severe limitations in interpreting the related outcomes from studies have been carefully elsewhere reported.[8]

As an example, the methods to calculate the optimal AVD values by using the QuickOpt and the SmartDelay algorithms have been reported (see Figure 1).

Clinical Impact Of IEGM Optimization Methods In-Clinic Optimization

Two big trials investigated the impact of using in-clinic IEGM-based methods. The two trials considered the hemodynamic[9] (SMART-AV; left ventricular end systolic volume, LVESV, at 6-month FU) and clinical[10,11] (FREEDOM, Packer's combined endpoint[12] at 12-month FU) effects of one - or more - optimization procedures when carried-out during FU visits (any automatic periodic optimization procedures was available in those devices).

More specifically, the SMART-AV study compared the use of the SmartDelay AV-optimization algorithm vs. echo-optimized AV delay vs. nominal settings (randomized 1:1:1 design), whereas the FREEDOM trial compared the use of the QuickOpt algorithm vs. empiric or echo-optimized settings (randomized 1:1 design).

Both trials did show a very satisfactory usability and safety profiles (both algorithms were shown to be safe and easy-to-use), but efficacy performances at 6- or 12-month FU[9,10] did overlap (concept of NON-Inferiority) with those observed in the routine clinical practice (echo-guided optimization or empirical settings).

Among the main limitations of those big trials, it is helpful - to the purpose of this discussion - to mention: FREEDOM study: a) non-uniform treatment in the control arm (investigators could optimize empirically or by using traditional tools, mainly echo); b) no crosscheck between clinical outcome and cardiac remodeling (no echo long-term data), which could be of help in supporting or reinforcing the interpretation of results; c) no clear indications of the contribution from the single components of the combined endpoint, so that it is impossible to evaluate whether there is a trend in terms of isolated hard endpoints (defined as secondary endpoints).

SMART-AV study: a) short term follow-up data only (6 months) were available, and no crosscheck with convincing clinical outcomes (soft clinical endpoints only available); b) a trend in favor of AV optimization through SmartDelay device algorithm (vs. echo-optimization or nominal settings) was clearly identified, leading the authors to suspect the study was underpowered to show a significant difference in the primary endpoint.

In both trials the authors conclude, basing upon non-inferiority, that systematic CRT optimization is not an issue: "standard" or "pre-defined/out-of-the-box" settings are generally satisfactory to get an acceptable rate of response over-time. These conclusions can be acceptable only if 1-year after CRT implant we are satisfied with a rate of clinical response around 65-70%, meaning that the use of specific optimization functions during FU visits does not significantly impact on hemodynamic and clinical outcomes of patients treated with CRT (vs. a routine clinical management).

Ambulatory Optimization

In the ADAPTIV-CRT trial the authors evaluated the clinical effects of a novel IEGM-based algorithm[13] (Adaptive-CRT, Medtronic) to continuously adapt CRT delivery mode (LV-only pacing or BiV pacing) and timing settings (AVD, VVD) over time, according to the evolution of rhythm characteristics (heart rate, PR interval, AV block, …) and resulting IEGM recordings.

This trial[14] essentially showed - with a prospective randomized design - that the device-based algorithm is non-inferior in outcome measures (at 6-month FU) to echocardiography optimization methods.

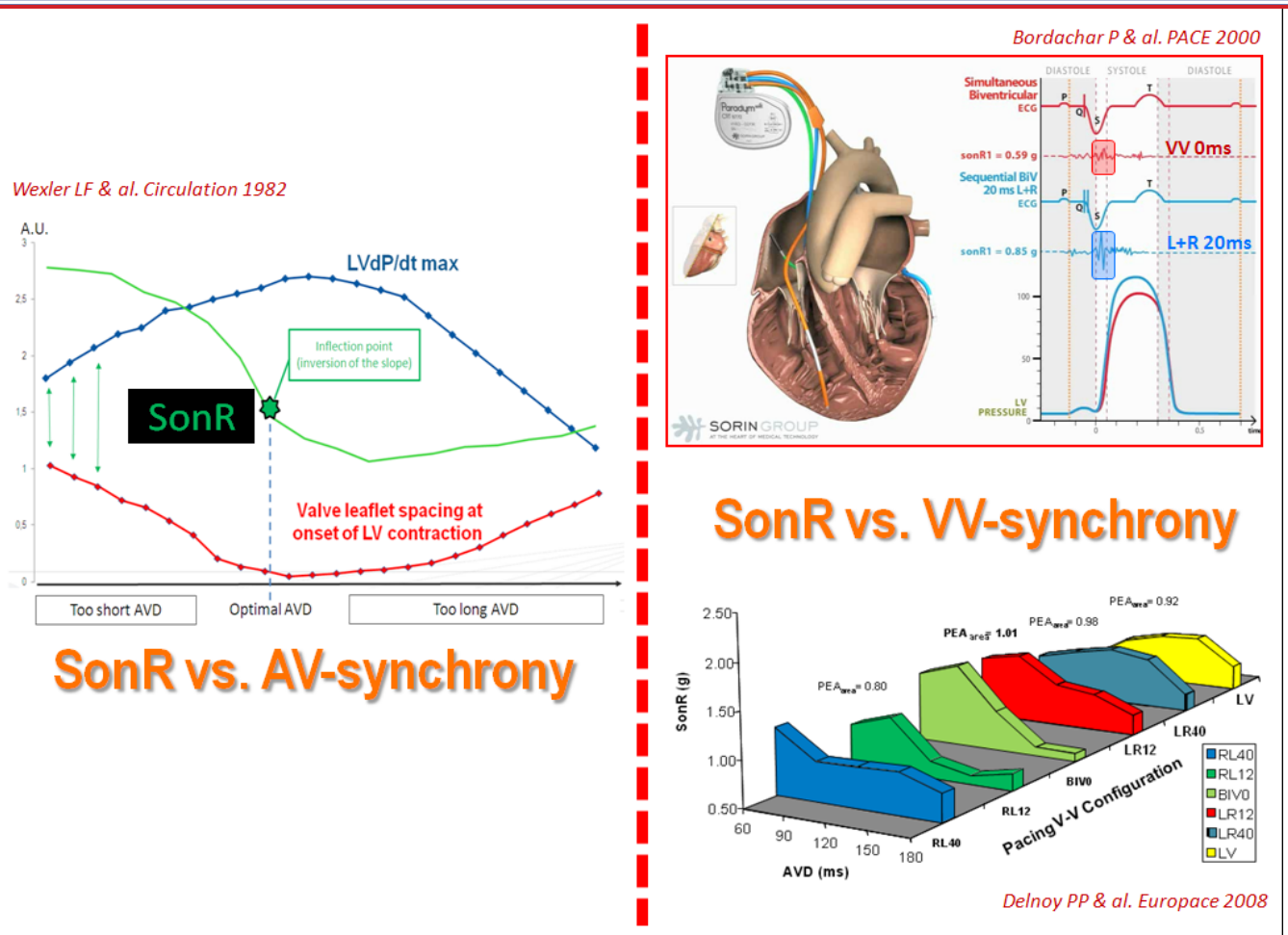

Figure 3: **Left panel: effects of AV-synchrony on the SonR signal, given by the overlapping effects of contractility (LVdP/dt max) and mitral leaflets movements on myocardial vibrations; this model allows to determine the optimal AVD by simply modulating the AV timings and interpolating the corresponding SonR curve. The optimal AVD corresponds to the inflection point of the SonR-sigmoid (green-curve).**
Right panel: effects of VV-synchrony on the SonR signal. For each VV delay, the SonR algorithm carries-out an AVD scanning, to determine which ventricular resynchronization configuration (VVD) provides with the maximum area under the curve (corresponding to the "best average contractility" over a spectrum of real-life variable filling conditions).

Another interesting ancillary finding of this trial was highlighted in a subgroup analysis: a significantly higher proportion of patients receiving primarily LV-only pacing (those with LBBB and no AV-block) had an improved clinical outcome vs. comparable patients from the echo-optimized arm.

In an attempt to further underline the relevance of an ambulatory optimization, results from a retrospective analysis were later reported[15] to compare clinical outcomes from the use of the algorithm vs. those from historical CRT cohorts. In this analysis (Figure 2) the algorithm shows a remarkable superiority at 6-month FU (rate of clinical response: 74% Adaptive-CRT vs 62% weighted average in historical CRT cohorts), leading authors to conclude that "the algorithm may be associated with additional improvement in clinical response compared with historical CRT".

Trying to explain such an impressive difference in outcomes, the authors suggest two main contributing factors in favor of the algorithm: a) ambulatory optimization (continuous re-adjustment of optimal AV and VV values); b) automatic switch between standard biventricular pacing and LV-only pacing (looking for fusion between LV pacing and spontaneous RV activation).

Once again, due to the severe disclosed limitations (short-term FU, missing 5% of the CRT-D device interrogations in the treatment group, limited data about safety), the authors acknowledge that "this hypothesis needs to be proven in prospective randomized trials".

Hemodynamic Optimization (SONR Endocardial Acceleration Sensor)

The endocardial acceleration technology and the meaning of the SonR signal have been widely described elsewhere.[16] This technology was preliminarly tested onboard on dual-chamber pacemakers, with a dedicated lead (equipped with the sensor in the tip) implanted in the right ventricle.

Essentially, an endocardial acceleration sensor picks-up myocardial vibrations mostly corresponding to the isovolumic contraction and relaxation phases. The SonR signal mirrors the amplitude of those vibrations, mimicking the content of a heart sounds recording (phonocardiogram); the amplitude of the SonR signal has been shown well-correlated with the LVdP/dt,[17] a marker of global myocardial contractility, in a variety of clinical conditions (healthy hearts, HF patients, induced ischemia, sinus rhythm and atrial fibrillation).

The correlation between SonR signal and LVdP/dt has been also shown independent upon the lead position: the latest generation of SonR system consists of a CRT-D (D = defibrillator) connected with an atrial dedicated lead.[18,19]

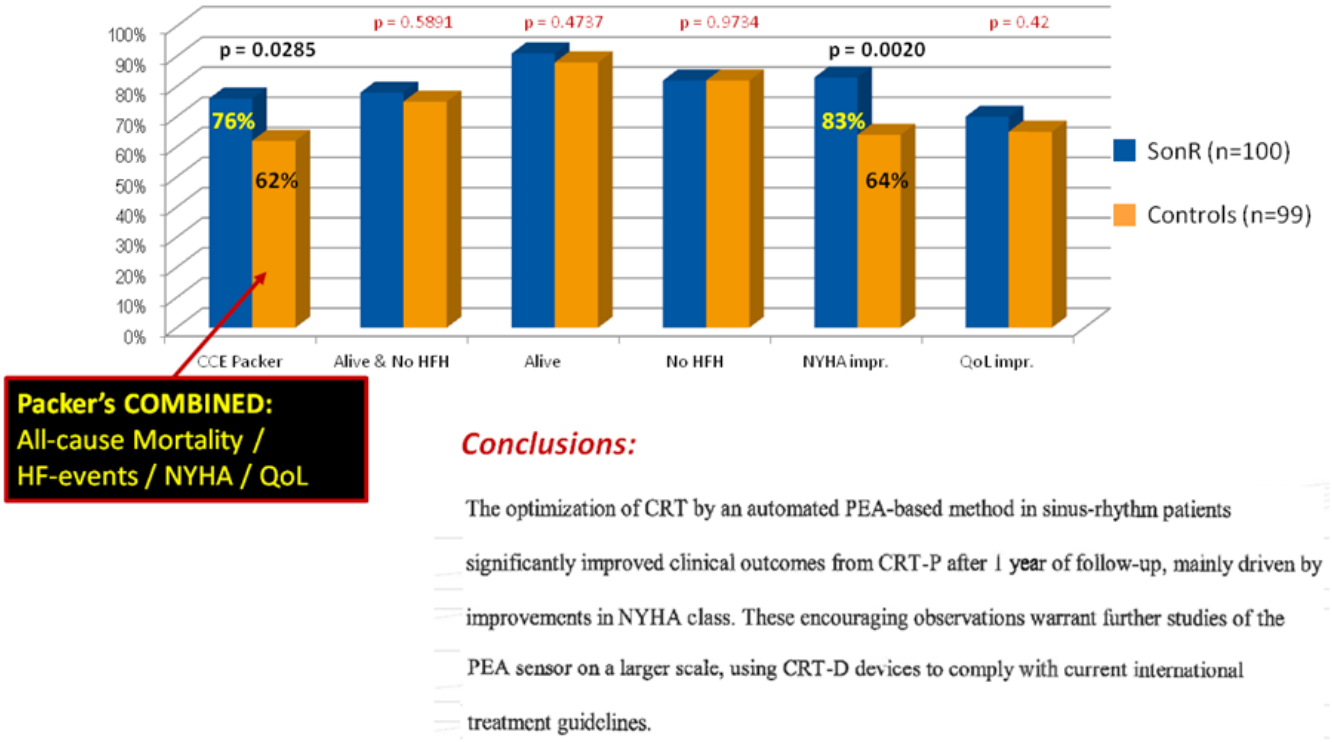

Figure 4: **Endpoints at 12-month follow-up visit observed in the CLEAR pilot study and related authors' conclusions. The rate of clinical responders (Packer's combined criterion) significantly differs among the two groups. Other hystograms represent secondary endpoints (single components of Packer's endpoint).**

The SonR signal derived from the sensor is transferred to and processed by the CRT-D software, allowing the extraction of signal features. Among various potential clinical applications, an algorithm has been developed for a repeatable automatic AVD and VVD values optimization in CRT devices.[16]

The SonR automatic optimization function (see Figure 3) allows to weekly optimize the VVD at rest, and the AVD values at rest and under effort (in atrial sensed or paced conditions), in order to get an optimal ventricular filling during daily life of recipient patients (not only in resting conditions). The whole optimization procedure can be carried-out during in-clinic FU visits (as for all the other device-based methods), but the clinician-user may also activate the function (CRT optimization = ON) so that the device automatically repeats the full optimization procedure on a weekly basis.

The automatic iteration of the optimization procedure is fully transparent to the user. The "one-button" feature makes this function extremely easy-to-use in the clinical practice.

Clinical Impact Of The SONR Hemodynamic Method

The CLEAR pilot study (run between 2004 and 2009 years) aimed to preliminarly compare the clinical outcome resulting from routine practice of the implanting Centers (SonR sensor OFF) vs frequent automatic optimization (SonR sensor ON).

Patients with CRT indications under optimal medical therapy (2003 Pacing/CRT Guidelines) in sinus rhythm, NYHA class III/IV and documented cardiac dyssynchrony, have been implanted with a CRT-P (P = pacemaker) system equipped with a SonR endocardial acceleration sensor realized into the tip of a right-ventricular lead (BEST sensor, Sorin Biomedica, Saluggia - Italy). The primary endpoint of the CLEAR study was Packer's clinical criterion,[12] combining all-cause death, HF events, NYHA functional class and QoL.

After implant and before hospital discharge, patients were 1:1 randomized into: a) SonR group: weekly automatic CRT optimization function ON; or b) Control group: patient management according to clinical practice and SonR automatic optimization function OFF. In the Control group the option to optimize (yes/no) CRT settings at FU visits (pre-discharge, 3-month, 6-month, 12-month) was left to physicians' discretion, as well as the optimization method to be used (alternative to SonR).

Data were gathered from n=268 included patients. Among them, n=238 have been randomized after implant. By analyzing data with an ITT (Intention-To-Treat) approach, n = 100 patients of the SonR group were compared with n = 99 patients in the Control group (Figure 4). The primary clinical endpoint was measured at 12-month FU visit:[20] a statistically significant difference was observed in favor of the SonR group (delta clinical response 14%: 76% SonR group vs. 62% Control group, p=0.0284, corresponding to a 23% relative clinical improvement in the SonR vs Control group).

Among the components of the Packer's endpoint (Figure 4), the clinical superiority observed in the SonR group was substantially driven by the NYHA class, which wasn't assessed by a blinded clinician. On the contrary, looking at hard components of the clinical endpoint (all-cause death and HF events), there is no significant difference among study groups (the pilot study wasn't clearly powered enough to this purpose).

The Ongoing "Respond-CRT" Trail

The latest SonR technology (released Sept. 2011: Paradym RF SonR CRT-D with atrial SonRtip lead; Sorin Group, Saluggia-VC, Italy) shows superior performance vs. previous releases, in terms of sensor reliability and algorithm robustness. A large-scale randomized double-blinded trial (RESPOND-CRT; clinicaltrials.gov id.:

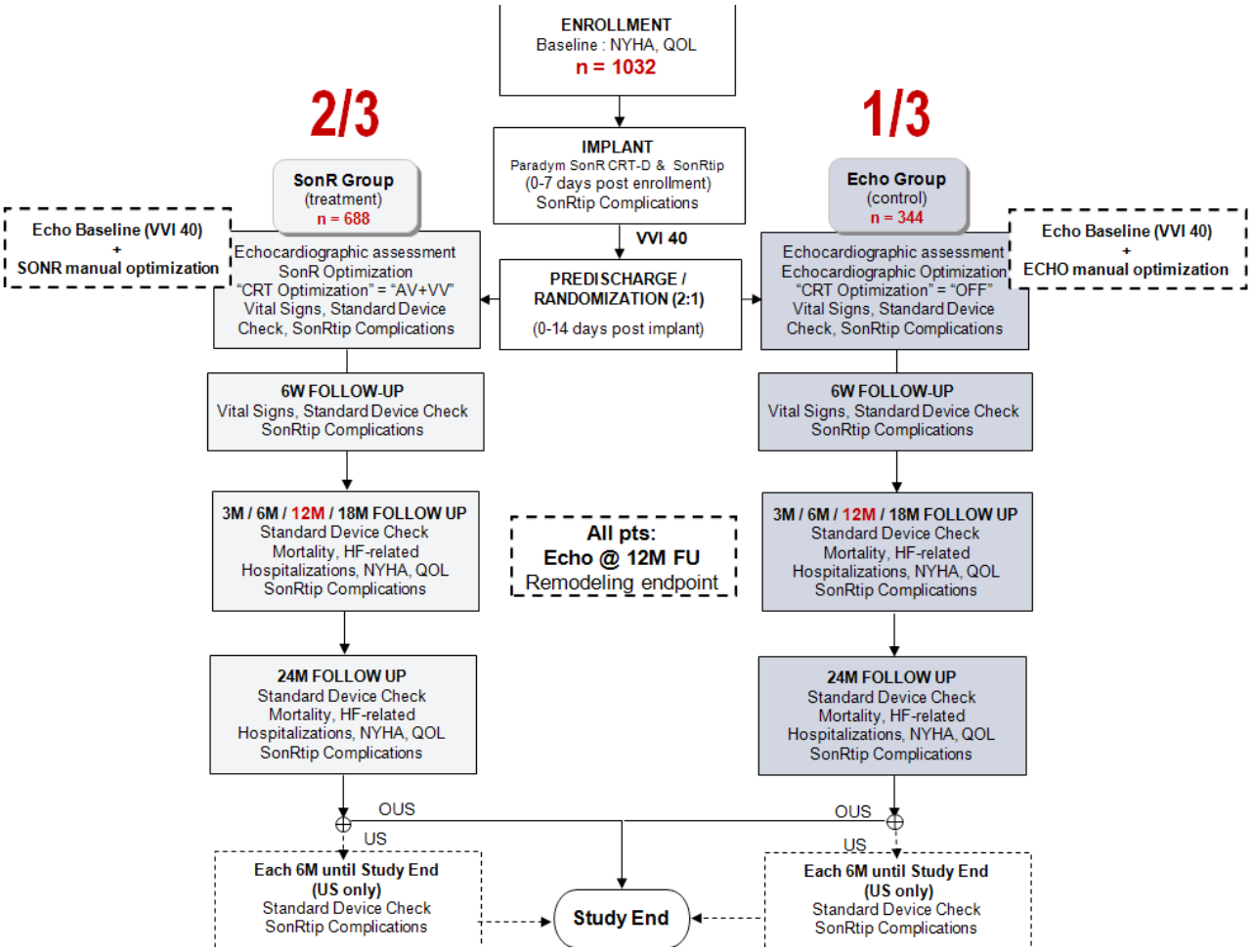

Figure 5: **Design of the prospective randomized double-blinded RESPOND-CRT trial. Patients are 2:1 randomized (respectively) to: left arm) activation of the SonR automatic CRT settings optimization function; right arm) single echo-optimization of CRT settings soon after implant (before hospital discharge) without activating the SonR automatic function. Clinical judgment during 2-year follow-up is provided by an independent group of blinded investigators.**

NCT01534234) started inclusions in January 2012, with a plan to stop inclusions at the end of 2014 year. This trial[21] is designed to prospectively measure the clinical benefit associated with the activation of the weekly automatic optimization (by using the SonR sensor) in patients with severe HF (NYHA class III or ambulatory class IV), sinus rhythm and a CRT-D indication (2012 HF Guidelines, class I and IIa). Among patients included in the RESPOND-CRT trial (Figure 5), those who are successfully implanted with the full SonR system are randomized in pre-discharge phase (ratio 2:1) to SonR group (activation of the SonR weekly automatic optimization) or Echo group (single Echo-optimization at pre-discharge; SonR weekly automatic optimization OFF). The clinical outcome is measured through the combined Packer's endpoint, with a clinical judgment derived by a double-blinded approach.

In order to be powered enough to show significant differences in terms of clinical outcome, n=1032 patients will be included in roughly 115 Centers worldwide (Europe, USA, Australia): a test of non-inferiority is planned at 12-month FU among study groups (SonR vs Echo). If the non-inferiority test is successfully reached, a superiority test will be also run on the same timeline (12-month FU visit), in order to show that an approach with a very frequent optimization of CRT settings leads to superior clinical outcome when compared with a single echo-optimization strategy.

Do "Frequent Optimizations" Improve Clinical Outcome?

An interesting post-hoc analysis of data from CLEAR patients has been recently published,[22] with the aim of retrospectively evaluate the impact of the "frequency" of optimization procedures on the primary clinical endpoint over long-term FU.

The same n=199 patients considered for the ITT approach[20] have been retrospectively grouped according to a criterion of "frequent optimization" (Frq-Opt) (performed during 3 consecutive FU visits: post-implant, 3-month, 6-month), whatever the method used (Echocardio or SonR) vs. "NON-frequent optimization" (Non-Frq-Opt) (0, 1 or 2 times among the FU visits up to 6 months FU).

Reported results are very intriguing: the frequency of optimization, whatever the hemodynamic method used (Echocardio or SonR) associates with an improved clinical outcome during long-term FU, when looking at Packer's combined endpoint (delta 24%: 85% Frq-Opt vs. 61% Non-Frq-Opt, p<0.001; 39% relative clinical improvement), or at risk of hard events (Kaplan-Meier curves, risk of all-cause death and/or HF events at 1-year FU, 54% relative reduction Frq-Opt vs. Non-Frq-Opt).

Although the above results have to be very carefully interpreted (modest sample size and retrospective nature of data comparison), the reported evidences pave the way to develop research programs around technologies supporting the concept of "frequent CRT opti-

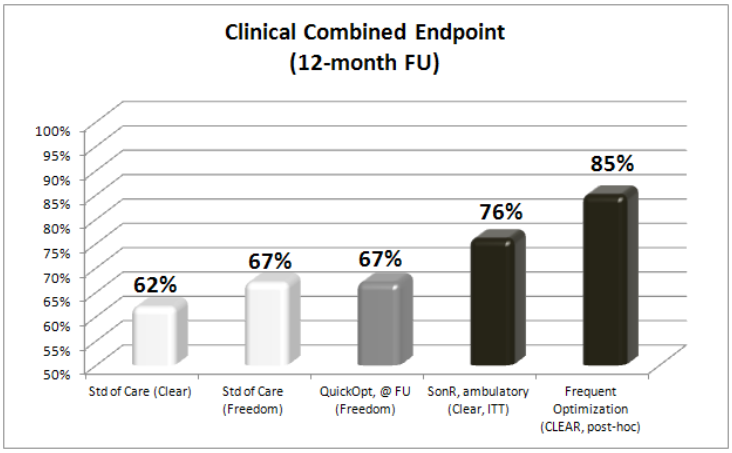

Figure 6: **Rate of clinical response at 12-month follow-up (Packer's combined criterion) among group of CRT patients in the CLEAR and FREEDOM trials. The comparison is purely qualitative (different populations, different study design, etc.); however, the overall impression is that a systematic optimization (ambulatory repeated procedures over time) provide patients with a better clinical outcome (to be prospectively confirmed by ongoing trials).**
References: CLEAR ITT (Intention-To-Treat), ref. [20]; FREEDOM, ref. [11]; CLEAR post-hoc, ref.[22]

mization" as a gold-standard in the clinical practice of CRT patients management.

When testing CRT settings optimization approaches from a long-term clinical standpoint, a barely qualitative comparison of the most significant experiences (mostly FREEDOM and CLEAR; populations not fully overlapping, though basically consisting of patients with sinus rhythm and advanced HF in NYHA class III/IV) suggest that using hemodynamic methods and frequently re-assessing optimal CRT settings could contribute to improve the rate of clinical response over long-term FU vs. IEGM methods or standard clinical practice (Figure 6). Of course, this "feeling" must be confirmed by conducting dedicated prospective trials in homogeneous populations, powered enough to get statistical significance.

Conclusion:

In patients treated with CRT, procedures to optimize device settings have been shown to acutely improve hemodynamics. Echocardiography still remains the gold-standard method to optimize CRT settings, despite several limitations (time- & resource-consuming, limited reproducibility, intra- & inter-operator dependency, difficult to be repeated over-time) making it only occasionally applicable to the routine clinical management of all CRT patients.

Device-based methods using IEGM formulas lead to significant result of non-inferiority (clinical and/or hemodynamic) vs. clinical practice or traditional echocardiography methods. The use of the automatic hemodynamic SonR-based method (endocardial acceleration sensor, correlated with LVdP/dt max, marker of global myocardial contractility) in the CLEAR pilot study portends a certain degree of clinical superiority vs. clinical practice. A post-hoc analysis in the same group of CLEAR patients suggests, despite the retrospective nature of this comparison, that a frequent optimization of CRT settings associates with an improved clinical outcome over long-term FU.

A significant contribution will be given by the ongoing "RESPOND-CRT" trial, whose goal is to prospectively assess (on a large-scale and with a double-blinded approach) the clinical impact of the automatic SonR-based hemodynamic method over long-term FU.

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